Hepatitis C Virus Infection

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Epidemiology

Prevalence and Incidence Estimates

Hepatitis C virus (HCV) is an enveloped, single-stranded RNA virus of the Flaviviridae family with seven known genotypes and 84 subtypes, with genotypes 1 and 3 being most common worldwide.[1-3] It is the most commonly reported bloodborne infection in the United States and is a leading cause of liver-related morbidity and mortality, particularly among people with HIV. In 2019, the estimated global prevalence of chronic HCV infection was 58 million (0.8% of general population), a decline from previous estimates of 71 million in 2015.[4] In the United States, updated estimates for 2013 to 2016 are that approximately 4.1 million people were HCV antibody positive (past or current infection; 1.7% of all adults); 2.4 million were HCV RNA positive (current infection; 1% of all adults).[5] Comparable data from 2003 to 2010 showed that 4.6 million people were antibody positive and 3.5 million were living with current HCV infection.[6] These updated lower prevalence estimates reflect interval trends, including increased cures with new treatment options and increasing death rates due to aging. However, these may be offset by increases in incident cases due to the opioid crisis in vulnerable counties.[7,8] Despite variable state-level surveillance practices,[9] Centers for Disease Control and Prevention (CDC) surveillance data from 2019 show regional differences in incidence and prevalence, increasing rates in rural areas, ongoing racial/ethnic disparities, and changing demographics, including a bimodal distribution of infections with peaks at 29 years and at 59 years of age.[10] Attributable mortality is highly variable among states and counties.[11]

Given the shared transmission routes between HIV and HCV, estimates of the burden of HCV infection in people with HIV (HIV/HCV coinfection) have been highly variable depending on the comprehensiveness of databases analyzed. A global systematic review and meta-analysis of studies published between 2002 and 2015 estimated that there were 2.3 million cases of coinfection worldwide, with 1.3 million (58%) attributed to persons who inject drugs; this translates to HCV coinfection prevalence of 6.2% among people with HIV.[12] Compared with people without HIV, the odds of HCV infection in people with HIV are six times higher. The prevalence of HCV infection among people with HIV is distributed in the following subgroups: people who inject drugs (82.4%), men who have sex with men (MSM, 6.4%), and those who are pregnant or heterosexually exposed (2.4%).[12] Estimates of HCV coinfection in the United States[10] have been cited as 21% but have ranged from 6% to 30% with high variability based on the distribution of HIV transmission risk factors.[13,14] In the United States, it is estimated that 62% to 80% of people who inject drugs who have HIV also have HCV infection.[10]

The availability of highly effective treatments for HCV infection has led to national and global initiatives aimed at HCV elimination in general and in high-risk persons, such as those with HIV coinfection. The World Health Organization has developed targets for countries to achieve HCV elimination by 2030: diagnosing 90% of those with chronic infection and curing 80% of those diagnosed.[4] The CDC *Division of Viral Hepatitis 2025 Strategic Plan* aims to increase HCV cure to >85% by 2030.[15] The use of an HCV cascade of care has shown that there are ongoing gaps to attaining cure encompassing screening, initiating and completing treatment, and preventing

reinfection.[16,17] Worldwide, 15.2 million (26.2%) out of an estimated 58 million people knew their HCV status by the end of 2019.[18] With progress in direct antiviral treatments, 9.4 million people received HCV treatment, with the vast majority cured, between 2015 and 2019.[18] Micro-elimination efforts to scale-up treatment as prevention among people with HIV have successfully demonstrated that such efforts can decrease hepatitis C incidence.[19-24]

Transmission Routes

Both HIV and HCV can be transmitted by percutaneous exposure to blood or blood products, sexual intercourse, and perinatal transmission; however, the relative efficiency of transmission by these routes varies substantially.[25] HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes.[26,27] Transmission via injection drug use remains the most common mode of acquisition in the United States, while transmission through contaminated blood products is now rare. Health care–associated transmission of HCV also can occur because of improper reuse of parenteral medications and equipment.[28] Other factors that have been associated with HCV infection include accidental occupation-related needlestick injuries, intranasal cocaine use, chronic hemodialysis, and tattoo placement.

Multiple outbreaks of acute HCV infection in MSM demonstrate that sexual transmission is an important mode of acquisition in this population. Risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted infections (STIs).[29-32] Evidence for increasing HCV incidence and prevalence in HIV-negative men seen in HIV pre-exposure prophylaxis (PrEP) clinics has led to current recommendations to monitor for acute HCV infection and routinely test for HCV as part of PrEP care.[33-35] Heterosexual transmission of HCV is uncommon but more likely in those whose partners have HIV/HCV coinfection.[16,36-38]

Perinatal transmission of HCV infection occurs in approximately 7% and 12% of infants born to HCV-seropositive and RNA-positive mothers without and with HIV infection,[39-41] respectively, with possible decreased transmission risk for women with HIV receiving antiretroviral treatment.[42]

Clinical Manifestations

Both acute and chronic HCV infections are usually minimally symptomatic or asymptomatic. Fewer than 20% of patients with acute infection have characteristic symptoms, including low-grade fever, mild right-upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels may be the only laboratory finding during acute and chronic infection. Recognition of acute HCV infection in patients with new-onset liver enzyme elevations is clinically important; early initiation of HCV treatment can lower the likelihood of poorer outcomes and prevent transmission to others (treatment as prevention).[43-45]

Cirrhosis develops in 20 to 40% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable.[46-48] Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use.[47,49] HIV coinfection adversely affects the course of HCV infection, resulting in significantly accelerated progression of liver disease to cirrhosis, particularly in those with advanced immunodeficiency[50,51] (CD4 T lymphocyte [CD4] count <200 cells/mm^3). Further, coinfected patients with cirrhosis progress more rapidly to life-limiting outcomes—such as end-stage liver

disease and hepatocellular carcinoma (HCC)—than those who are HCV mono-infected,[52,53] even if they are virally suppressed.[54] Because of its high prevalence and accelerated progression, HCV infection was a leading non-AIDS cause of death in people with HIV before the advent of highly effective direct-acting antivirals.[55-57] In addition to liver disease, HCV may be associated with symptomatic vasculitis due to cryoglobulinemia (largely affecting the skin or joints), renal disease (membranoproliferative glomerulonephritis), and porphyria cutanea tarda.

Diagnosis

On entry into HIV care, all patients should undergo routine HCV screening **(AII).** Initial testing for HCV should be performed using a U.S. Food and Drug Administration (FDA)-approved immunoassay licensed for detection of antibody to HCV (anti-HCV) in blood.[58,59] For at-risk HCV-seronegative individuals, specifically MSM or persons who inject drugs, HCV antibody testing, using an FDA-approved immunoassay, is recommended annually or as indicated by clinical presentation, risk activities, or exposure **(AII).** Concordantly, both the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV guidance and CDC PrEP guidelines also recommend HCV serologic testing at baseline and every 12 months for MSM, transgender women, and people who inject drugs.[59,60] Nucleic acid testing for HCV RNA is recommended in settings where acute infection is suspected or in persons with known prior infection cleared spontaneously or after treatment **(AIII).**

False-negative anti-HCV antibody results are possible among people with HIV but uncommon (2% to 4%), and more likely to be seen in patients with advanced immunosuppression[61] (CD4 cell count <200 cells/ mm^3). HCV RNA testing should be performed in those patients with risk factors or unexplained ALT elevation. In addition, negative anti-HCV antibody results can occur during acute infection. Following acute HCV infection, the duration of the window period prior to seroconversion is highly variable, ranging from 2 weeks to more than 24 weeks,[62,63] with antibody response in most persons detectable at 8 to 12 weeks. Serum ALT levels are frequently elevated early in the course of HCV infection, and high ALT levels should prompt testing for HCV RNA if serologic test results are negative or indeterminate in individuals at risk of HCV infection.[64]

Individuals who test positive for HCV antibody should undergo additional diagnostic testing by using a sensitive quantitative assay to measure plasma HCV RNA level and confirm current infection **(AI).** This should preferentially be done as an automatic reflex to HCV RNA testing of the leftover serum from the blood draw for antibody testing to facilitate diagnosis.[65] Reinfection can occur in both seropositive individuals who spontaneously clear their infection or those who achieve a sustained virologic response to treatment. Diagnosing a new active infection will require HCV RNA testing in such individuals **(AII).**

Preventing Exposure

The primary route of HCV transmission is blood-to-blood contact, most commonly from sharing drug-injection equipment or paraphernalia (i.e., “cookers,” filters, or water) previously used by an infected person with HCV. Prevention approaches for persons who inject drugs include harm-reduction encompassing opioid agonist therapy and syringe services programs to avoid the reuse or sharing of syringes, needles, water, cotton, and other drug preparation equipment.[66,67] Both needle and syringe exchange programs and opioid substitution therapy have been shown to reduce the risk of HCV acquisition in people who inject drugs.[67,68] HCV also can be transmitted sexually, especially among MSM with HIV.[69] Risk factors for sexual HCV acquisition include unprotected anal receptive

intercourse, fisting, sharing of sex toys, ulcerative STIs, and use of methamphetamine or other sex-enhancing drugs (injection or otherwise).[70,71]

Patients should be counseled regarding the risk of sexual HCV acquisition **(AII).** Those with multiple sex partners or STIs should be advised to use barrier protection to reduce their risk of STIs including hepatitis C infection **(AII).**

Preventing Disease

There is no available vaccine or recommended post-exposure prophylaxis to prevent HCV infection.[72,73] Following acute HCV infection, chronic infection can be prevented within the first 6 to 12 months after infection through antiviral treatment; high rates of viral clearance have been observed with HCV treatment during the acute phase of infection.[74,75]

Because most patients with acute HCV infection may transmit to others and are at risk for loss to follow-up, immediate treatment with the same regimens recommended for chronic HCV should be offered **(AIII).**[44,76] Specific treatment regimens in acute infection are the same as those recommended for chronic HCV infection and are detailed in the Treating HCV section.

People with HCV infection should be tested for previous or concurrent hepatitis B virus (HBV) infection because coinfection with HBV is associated with increased morbidity **(AII).** Those without evidence of immunity to HBV infection should be vaccinated (see the Hepatitis B Virus Infection section) **(AII).** Likewise, because acute hepatitis A virus (HAV) infection is more likely to be fulminant in persons with HCV infection,[77] these patients should be screened for immunity (HAV immunoglobulin G or antibody total) and non-immune persons should be vaccinated **(AII).**

People with HCV infection should be counseled about methods to prevent liver damage by avoiding any alcohol consumption (because alcohol accelerates progression of liver disease), limiting ingestion of potentially hepatotoxic medications (e.g., acetaminophen should be limited to <2 g/day for those with acute infection or bridging fibrosis/cirrhosis), and avoiding iron supplementation in the absence of documented iron deficiency.[78]

People with HIV/HCV coinfection with cirrhosis are at risk of life-threatening complications and should be managed in consultation with a gastroenterologist or hepatologist. In particular, individuals with cirrhosis should undergo serial screening for HCC; current guidelines recommend performing ultrasonography at 6-month intervals, although the optimal screening strategy is unknown **(AIII).**[79] Because of its relatively poor specificity and sensitivity, serum alfa-fetoprotein is an adjunct to ultrasonography but should not be the sole screening method.[79] HIV infection is not a contraindication to liver transplantation; accordingly, coinfected patients with decompensated liver disease and/or early HCC may be considered for transplantation at specialized transplant centers.

Although earlier studies focused on the potential for antiretroviral (ARV)-associated liver injury with certain agents, more recent studies have found that effective HIV treatment is associated with reduced risk of liver disease progression, though not to levels of persons with HCV infection without HIV.[54,80] Coinfected patients should be treated in accordance with the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.

Treating HCV Infection

Introduction

Direct-acting antiviral (DAA) regimens for HCV infection have become standardized with one of two pangenotypic, highly efficacious and well-tolerated antiviral treatment regimens, which are the preferred therapy for HCV infection for almost all persons with HIV and HCV. Clinicians can refer to the most recent AASLD/IDSA HCV treatment guidance.

The goals of therapy, treatment regimen, and monitoring parameters for patients with HIV/HCV coinfection are similar to those recommended for patients with HCV mono-infection. However, people with HIV were historically considered a "special population" with regard to HCV treatment. This designation was rooted in inferior responses to interferon-based treatment for those with HIV.[81,82] The arrival of initial DAA regimens narrowed the gap in response to treatment but continued to present significant drug–drug interaction considerations and, in some circumstances, warrant extended treatment durations.

Simplified approaches to HCV treatment have emerged as a means to facilitate treatment by non-specialist providers and increase treatment uptake for the majority of persons with HCV infection. In general, simplified approaches to HCV treatment apply to treatment-naive persons without cirrhosis and encompass minimal baseline testing (with omission of genotype), standardized treatment approaches using pangenotypic regimens, no on-treatment testing or in-person follow-up, and limited follow-up to confirm sustained virologic response (SVR).

Several factors now allow people with HIV to access simplified HCV treatment recommendations. The emergence of unboosted integrase strand transfer inhibitor (INSTI)-based ARV regimens has eliminated clinically significant drug interactions with current first-line DAA regimens. Additionally, the improved safety profile of tenofovir alafenamide (TAF) combined with safety data in the setting of boosted ARV regimens during coadministration with DAAs obviate the need for enhanced toxicity monitoring for people with HIV in most instances. Finally, accumulation of clinical efficacy data and the necessity of expanding treatment access support the use of simpler standardized treatment approaches initially validated in HCV mono-infected populations for those with HIV. Based on these developments and the emergence of pangenotypic DAA regimens, treatment of HCV can be approached using simplified protocols for the majority of people with HIV.

Published clinical trial data directly support a simplified approach to HCV treatment, including for people with HIV. The AIDS Clinical Trial Groups (ACTG) A5360 study (MINMON) evaluated an approach consisting of limited baseline testing and supply of the entire 84-tablet (12-week) sofosbuvir/velpatasvir treatment regimen in 399 participants, including 166 with HIV.[83] All participants were HCV treatment-naive, compensated cirrhosis was allowed, and no pre-treatment HCV genotyping was performed. No on-study laboratory monitoring or in-person follow-up was conducted. The SVR after 12 weeks post-treatment (SVR12) was 95% overall (95% CI, 92.4% to 96.7%) and 95% in the subset of people with HIV (157/166).

The SMART-C study randomized participants to either a standard 8-week treatment with glecaprevir/pibrentasvir (n = 127), which included in-person follow-up at weeks 4 and 8 with medication refill required at week 4, or to a simplified approach (n = 253) that omitted the on-treatment visits with all medication dispensed at initiation.[84] Persons with previous HCV treatment or cirrhosis were excluded and only a small number of people with HIV (n = 27) were included. A

modified intention-to-treat analysis (excluding lost to follow-up and missing SVR12 results) established non-inferiority of the simplified approach with SVR12 of 97% (233/241) compared with 98% (121/123) in the standard-approach arm. No difference in response was seen by HIV status.

Staging and Monitoring

While a pre-HCV treatment assessment of patient readiness for therapy should be completed, with an indication that reasonable adherence can be expected, HCV DAA therapy should not be withheld solely due to perceived lack of adherence with HIV therapy or untreated HIV infection **(BIII).** Evidence suggests the level of adherence needed for HCV cure is more modest than that required to maintain HIV viral suppression.[85-87] In addition, despite a lack of HIV control, patients may be uniquely motivated by the potential for HCV cure, thereby increasing the likelihood of successful treatment.

Additional fibrosis stage assessment may be indicated in people with HIV with an indeterminate FIB-4 (1.45–3.25) score, particularly if cirrhosis is suspected **(BIII).** Additional blood- or serum-based assays for fibrosis staging **are not recommended** because they provide little benefit over FIB-4 **(BII).**[88,89]

Non-invasive ultrasound-based (e.g., shear wave elastography or vibration controlled transient elastography) or imaging-based (e.g., magnetic resonance elastography) modalities are recommended if available **(BII).** Liver biopsy **is no longer recommended** for liver fibrosis staging related to HCV infection unless there is another indication to obtain one **(AII).** Treatment should not be withheld if access to additional staging modalities is not readily available **(AIII).**

Simplified Approach to HCV Treatment

The current AASLD/IDSA HCV guidance for simplified HCV treatment of treatment-naive adults (without cirrhosis or with compensated cirrhosis) excludes persons with HIV. The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommends an approach that allows most people with HIV to qualify for simplified HCV treatment. This simplified approach is appropriate except in certain people with HIV with conditions noted in **Box 1.** Such exclusions highlight the importance of particular ARV regimens with significant drug–drug interactions with ARVs (see below).

Box 1. Characteristics of People with HIV for Whom Simplified Hepatitis C Virus Treatment Is Not Recommended[a]

1. Prior HCV treatment (Reinfection after prior successful therapy is not an exclusion.)
2. Decompensated cirrhosis[b]
3. TDF-containing regimen with an eGFR <60mL/min
4. On efavirenz, etravirine, nevirapine, or boosted HIV-1 protease inhibitors[c]
5. Untreated chronic HBV infection
6. Pregnancy

[a] People with HIV and HCV infection who meet these exclusion criteria should be treated for HCV following standard approaches (see the AASLD/IDSA HCV Guidance).

[b] Including, but not limited to, current or prior variceal bleeding, ascites, or hepatic encephalopathy

[c] People with HIV on boosted protease inhibitors are not eligible for treatment with glecaprevir/pibrentasvir and may require on-treatment monitoring.

Key: eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; TDF = tenofovir disoproxil fumarate

A limited pre-treatment assessment for people with HIV is essentially the same as for people without HIV who qualify for a simplified approach **(Box 2) (AIII).** Key components are documentation of active HCV infection and initial assessment of liver fibrosis stage. Determination of HCV genotype prior to treatment is not necessary in treatment-naive patients, with the exception of persons with compensated cirrhosis who are planned for treatment with sofosbuvir/velpatasvir. In this case, if genotype 3 HCV infection is identified, additional testing for resistance-associated substitution (RASs) is required before treatment with sofosbuvir/velpatasvir. Notably, HIV parameters (i.e., HIV RNA or CD4 count) are not required to determine eligibility for a simplified approach. The efficacy of HCV DAA treatment for people does not appear to be compromised at lower CD4 counts.[90-92]

Box 2. Pre-treatment Assessment Under Simplified Approach

1. Creatinine, liver function tests, and complete blood count
2. HCV RNA
3. Hepatitis B surface antigen
4. Initial fibrosis staging with FIB-4 (FIB-4 calculator)[a]
5. Medication and drug interaction review
6. HCV genotype required if cirrhosis is present

[a] Additional testing may be required if results are indeterminate (see text).

Key: HCV = hepatitis C virus

Drug–Drug Interactions

Drug interactions with ARVs pose less of a constraint on DAA use to treat HCV infection in people with HIV given the prominence of unboosted INSTI and TAF among first-line ARV regimens.[93] A comprehensive review of drug interactions between ARVs and antivirals for hepatitis C can be found within the Hepatitis C Virus/HIV Coinfection section of the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Interactions of clinical significance pertaining to the recommended DAA regimens are highlighted here and in **Table 4.**

Efavirenz coadministration results in a significant decrease in glecaprevir, pibrentasvir, and velpatasvir exposures.[94,95] People with HIV on an efavirenz-containing regimen are not eligible for simplified DAA treatment approaches **(Box 1)** and generally require an ARV switch prior to DAA treatment **(AII).**

Given similar pharmacologic profiles, including cytochrome P450 (CYP) enzyme induction, nevirapine and etravirine are also not recommended for coadministration with HCV DAAs, including glecaprevir/pibrentasvir and sofosbuvir/velpatasvir **(AII).**

Ritonavir- or cobicistat-boosted protease inhibitors significantly increase glecaprevir and pibrentasvir exposure[94]; people with HIV on boosted protease inhibitor (PI)–based ARV regimens were not included in registrational trials of glecaprevir/pibrentasvir and coadministration is not

recommended **(BII).**[96] Boosted protease inhibitors also increase velpatasvir exposure, which in turn increases tenofovir plasma exposure particularly when administered as TDF.[95] People with HIV on boosted ARV regimens were included in sofosbuvir/velpatasvir registrational trials, and the combination was not associated with increased adverse events.[97]

Given these considerations, sofosbuvir/velpatasvir can be co-administered with boosted ARV regimens **(AII);** TAF-based regimens are preferred. People on TDF-containing boosted ARV regimens are not eligible for simplified HCV treatment if their estimated glomerular filtration rate is <60 mL/min because monitoring on treatment is recommended **(AII).**

Summary of Major Drug Interactions Between HIV and HCV Antivirals

HIV Antivirals	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
EFV, ETR, NVP, and other strong CYP 3A4 and P-gp inducers	Significant decrease in glecaprevir and pibrentasvir concentrations (avoid)	Significant decrease in velpatasvir concentrations (avoid)
PI/r, PI/c, unboosted ATV	Significant increase in glecaprevir and pibrentasvir concentrations (avoid)	Boosted PIs may increase velpatasvir concentrations, but no significant adverse events in clinical trial Coadministration allowed
TDF, TAF	Coadministration allowed	TAF preferred If TDF is used with boosted PIs if GFR <60 mL/min, monitoring is recommended.
RPV, DOR, EVG/c, RAL, BIC, DTG, ABC, FTC, 3TC, MVC	Coadministration allowed	Coadministration allowed

Key: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CYP = cytochrome P450; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GFR = glomerular filtration rate; FTC = emtricitabine; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; P-gp = p-glycoprotein; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

HCV Treatment Regimens

In HCV treatment-naive persons **without cirrhosis,** the recommended DAA regimens are either—

- Glecaprevir/pibrentasvir fixed dose combination (FDC) (100-mg/40-mg tablet), three tablets daily for 8 weeks **(AI)**

OR

- Sofosbuvir/velpatasvir FDC (400-mg/100-mg tablet), one tablet daily for 12 weeks **(AI)**

As noted in **Box 1,** these recommendations do not apply to HCV treatment–experienced patients because some of these individuals may require other DAA combinations and/or consultation with an expert. Persons meeting other criteria listed in **Box 1** should be treated according to standard approaches. Clinicians can refer to the most recent HCV treatment guidance for recommendations.

Primary data supporting the efficacy and safety of the two recommended treatment regimens in people with HIV come from registrational trials. In the ASTRAL-5 study, 12 weeks of sofosbuvir/velpatasvir without ribavirin was given to 106 people with HIV, including 19 with cirrhosis.[97] The SVR12 was 95% by intention-to-treat analysis with only two of five failures due to confirmed viral relapse. All participants with cirrhosis were cured. The EXPEDITION-2 study evaluated glecaprevir/pibrentasvir 300 mg/120 mg in 153 people with HIV with duration determined by cirrhosis status, with 137 non-cirrhotic participants treated for 8 weeks and 16 with cirrhosis treated for 12 weeks.[96] By intention-to-treat analysis, SVR12 was 98%, including 135 out of 137 participants without cirrhosis and 15 out of 16 participants with cirrhosis. The only confirmed virologic failure was virologic breakthrough at week 8 in a participant with genotype 3 and cirrhosis. Both regimens were well tolerated with low rates of discontinuation and no severe treatment-associated adverse events.

If compensated cirrhosis is present and sofosbuvir/velpatasvir is the planned regimen, then pre-treatment HCV genotyping is recommended **(AII).** If HCV genotype 3 is identified, NS5A resistance testing and modification of the sofosbuvir/velpatasvir regimen or selection of an alternative therapy may be necessary (for a full discussion, see the HCV treatment guidance). For all other genotypes or if glecaprevir/pibrentasvir is being used (regardless of genotype), no modification to the treatment regimen is required in the setting of compensated cirrhosis **(AIII).** The lower-strength recommendation for use of 8 weeks of glecaprevir/pibrentasvir in the setting of cirrhosis stems from a lack of prospective trials evaluating this duration in people with HIV and cirrhosis; 12 weeks of glecaprevir/pibrentasvir may be used in this setting **(CI).** The EXPEDITION-8 trial evaluated 8 weeks of glecaprevir/pibrentasvir in 343 participants with compensated cirrhosis and without HIV infection.[98] The intention-to-treat SVR12 was 98% and >99% in a per protocol analysis. The lone virologic failure was in genotype 3 infection yielding a per protocol SVR12 in this group of 98% (60/61). Data from real-world experience of use of 8 weeks of glecaprevir/pibrentasvir in the setting of cirrhosis were recently presented and included a small number of people with HIV.[99] Of the 20 people with HIV treated for 8 weeks, 19 out of 20 achieved SVR with no confirmed virologic failures.

Specific Treatment Situations

Acute HCV Infection Treatment

People with HIV are at risk for acute HCV infection. Given the public health implications in reducing onward transmission, in addition to benefit for the individual, HCV treatment should be started as soon as possible in this population **(AIII).**[21,44,100] The simplified treatment regimens outlined above are recommended in acute HCV infection **(AII);** shorter durations of therapy are currently being investigated. Patients who achieve viral clearance either spontaneously or after treatment should be counseled about the potential for reinfection.

Prior DAA Failure Retreatment

Despite the high cure rates associated with current DAA regimens, the large number of DAA treatments will inevitably result in an appreciable number of DAA failures. Persons with HIV were not included in the registrational trial of sofosbuvir/velpatasvir/voxilaprevir for retreatment of HCV infection[101]; nor were they included in initial prospective trials of either glecaprevir/pibrentasvir or sofosbuvir plus glecaprevir/pibrentasvir for HCV treatment of prior NS5A inhibitor containing DAA failures.[102,103] A follow-up prospective study comparing 12 weeks versus 16 weeks of

glecaprevir/pibrentasvir for genotype 1 sofosbuvir plus NS5A inhibitor failures did include a small number of people with HIV (~5%).[104] Similarly, published real-world experiences with retreatment of prior DAA failures are underrepresented with respect to people with HIV (all <5% except one with 15%).[105-108]

Drawing on the experience with initial DAA therapy of HCV infection, where people with HIV have nearly identical outcomes to persons with HCV infection alone, treatment approaches for DAA failures should be the same as those for persons with HCV mono-infection **(AIII).** Clinicians should refer to the most recent HCV treatment guidance for up-to-date recommendations.

Laboratory Monitoring and Post-Treatment Follow-Up

Laboratory monitoring while on treatment is not required for patients qualifying for the simplified treatment approach. However, documentation of HCV RNA levels at week 4 of therapy may be required by some payors prior to providing additional refills needed to complete therapy.

Effort should be made to document SVR (HCV RNA less than lower limits of quantification) at least 12 weeks after completion of therapy **(AI).** Patients without cirrhosis who achieve SVR do not require continued liver disease monitoring.

Periodic assessment for HCV reinfection should be done via HCV RNA testing on an at least yearly basis for those with ongoing risk behaviors or more frequently as dictated by clinical circumstances (e.g., new STI diagnosis or elevated liver enzymes) **(AII).**

In the setting of cirrhosis, hepatocellular carcinoma screening with liver ultrasound every 6 months should continue indefinitely **(BII).**

Special Considerations During Pregnancy

Testing for HCV infection should be performed during pregnancy to allow appropriate management for HCV-affected mothers during their pregnancy and after delivery and also to ensure their infants are identified as at risk for transmission and monitored **(AIII).**[109]

The rate of perinatal transmission has been reported at approximately 7% for infants born to mothers without HIV and 12% for infants born to mothers with HIV.[35,39,110] Due in large part to the opioid epidemic, more infants are born today with HCV infection than ever before[111,112]; thus, universal screening during each pregnancy, regardless of HIV status, is now the standard of care.[113] For the care of the infant, knowledge of exposure risk allows for screening for perinatal transmission.[114] During pregnancy, harm-reduction counseling and linkage to HCV care and treatment are important.[115]

Assessments for liver disease stage can be delayed until pregnancy related and postpartum changes have resolved. Individuals with known cirrhosis are at higher risks of complications during pregnancy, both for the individual and their infant. Hepatitis A and hepatitis B vaccines can be administered during pregnancy, and individuals who have not previously been vaccinated should receive them **(AII).**

Data are limited regarding the role of medical or surgical interventions to reduce the risk of perinatal HCV transmission. Nearly all studies, including those in individuals with and without HIV, have found that elective cesarean delivery does not reduce the risk of perinatal HCV transmission.[116-119]

Moreover, there is an increased risk of maternal morbidity associated with cesarean compared with vaginal delivery, particularly in the setting of maternal HIV infection.[120-123] Thus, while elective cesarean delivery in individuals with HIV/HCV coinfection can be considered based on HIV-related indications, data do not support its routine use for the prevention of HCV transmission.

The current standard of care for treatment of HCV infection, regardless of duration, is DAA combination therapy. In real-world studies, SVR rates are similar to those from registration trials,[124,125] and are consistently >90%. DAAs have not been sufficiently studied in pregnant women with HCV infection. In a pilot study of ledipasvir/sofosbuvir in pregnant women (without HIV infection), treatment was started in the end of the second/beginning of the third trimester and found to be safe and resulted in cure in nine women.[126] Pharmacokinetic measurements did not identify clinically significant changes.

Historically, while not studied in this population, DAA drugs have not demonstrated significant fetal toxicity concerns in animal studies, in contrast to when interferon and ribavirin were the standard of care. Interferon is no longer used for the treatment of HCV infection and ribavirin is used infrequently and usually in complex treatment or retreatment scenarios. Ribavirin is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia.

Ribavirin **should not be used** during pregnancy **(AII).** Women of childbearing potential and men receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy **(AIII).** Inadvertent pregnancy during paternal exposure was not associated with adverse events in two newborns.[127] For now, treatment with DAA during pregnancy **is not recommended (CIII);** more safety data are needed.

Recommendations for Treatment of Hepatitis C Virus Infections

For Treatment-Naive Patients Without Cirrhosis (Any Genotype or No Pre-Treatment Genotype)

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AI) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks (AI)

Note: Characteristics that exclude people with HIV from receiving simplified therapy are outlined in Box 1.

For Treatment-Naive Patients with Compensated Cirrhosis (Recommendations Based on Genotypes)

Genotypes 1, 2, 4–6

Preferred Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AIII) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks (AI)

Alternative Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 12 weeks (CI)

Genotype 3

Preferred Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AIII)

Alternative Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 12 weeks (CI) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily, with or without ribavirin for 12 weeks pending results of NS5A RAS testing (CI)

For Treatment of Acute HCV Infection

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AII) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks (AII)

Recommendations for treatment after DAA failure are not provided; see the corresponding section in the AASLD/IDSA HCV treatment guidance.

Key: AASLD = American Association for the Study of Liver Diseases; DAA = direct-acting antivirals; FDC = fixed-dose combination; HCV = hepatitis C virus; IDSA = Infectious Diseases Society of America; RAS = resistance-associated substitutions

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